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BEFORE THE BOARD OF PATENT APPEALS AND INTERFERENCES

Application Number: 10/757,803
Filing Date: January 14, 2004
Appellant(s): MCSWIGGEN ET AL.

Peter Haeberli
For Appellant

EXAMINER'S ANSWER

This is in response to the appeal brief filed 1/20/10 appealing from the Office action mailed 11/3/09.

(1) Real Party in Interest

A statement identifying by name the real party in interest is contained in the brief.

(2) Related Appeals and Interferences

The following are the related appeals, interferences, and judicial proceedings known to the examiner which may be related to, directly affect or be directly affected by or have a bearing on the Board's decision in the pending appeal:

Appeal No. 2009-2562, resulting from application No. 90/008,177 (Re-examination of US Patent 7,022,828).

The following US patent applications are currently on appeal and share common priority with the instant application:

USSN 11/502,875
USSN 10/693,059
USSN 11/487,788

(3) Status of Claims

The following is a list of claims that are rejected and pending in the application:

Claims 18-20 and 33-39 stand rejected and are presently pending.

(4) Status of Amendments After Final

The examiner has no comment on the appellant's statement of the status of amendments after final rejection contained in the brief.

(5) Summary of Claimed Subject Matter

The examiner has no comment on the summary of claimed subject matter contained in the brief.

(6) Grounds of Rejection to be Reviewed on Appeal

The examiner has no comment on the appellant's statement of the grounds of rejection to be reviewed on appeal. Every ground of rejection set forth in the Office action from which the appeal is taken (as modified by any advisory actions) is being maintained by the examiner except for the grounds of rejection (if any) listed under the subheading "WITHDRAWN REJECTIONS." New grounds of rejection (if any) are provided under the subheading "NEW GROUNDS OF REJECTION."

WITHDRAWN REJECTIONS

The following grounds of rejection are not presented for review on appeal because they have been withdrawn by the examiner: rejection under 35 USC 112, 2nd paragraph and Double patenting rejection.

(7) Claims Appendix

The examiner has no comment on the copy of the appealed claims contained in the Appendix to the appellant's brief.

(8) Evidence Relied Upon

5,998,203	Matulic-Adamic et al.	12-1999
5,898,031	Crooke	4-1999

Elbashir et al. (The EMBO Journal, 2001, Vol. 20, No. 23, pages 6877-6888)

Parrish et al. (Molecular Cell, Vol. 6, pages 1077-1087, 2000)

(9) Grounds of Rejection

The following ground(s) of rejection are applicable to the appealed claims:

Priority

Applicant's claim for the benefit of a prior-filed application under 35 U.S.C. 119(e) or under 35 U.S.C. 120, 121, or 365(c) is acknowledged. Applicant has not complied with one or more conditions for receiving the benefit of an earlier filing date under 35 U.S.C. 119(e) or 120 as follows:

The later-filed application must be an application for a patent for an invention which is also disclosed in the prior application (the parent or original nonprovisional application or provisional application). The disclosure of the invention in the parent application and in the later-filed application must be sufficient to comply with the requirements of the first paragraph of 35 U.S.C. 112. See *Transco Products, Inc. v. Performance Contracting, Inc.*, 38 F.3d 551, 32 USPQ2d 1077 (Fed. Cir. 1994).

The applications do not teach the instant combination of limitations: each strand is 18-27 nucleotides in length, wherein 18-23 are complementary to each other and at least 18 nucleotides of the antisense strand are complementary to a target; in combination with 10 or more pyrimidine nucleotides of the sense and antisense strand being chemically modified with 2'-deoxy, 2'-O-methyl, or 2'-deoxy-2'-fluoro; and in combination with the elements of the dependent claims.

Upon a review of 60/358,580, for example, the instant length limitations are disclosed on page 11 as being specific for the structures of Formula I, II, III, and IV; wherein the instant modification schematics are elements of other embodiments.

Although applicant points to support for the instant chemical modifications of claim 18 at page 30, lines 2-7 (as well as in the priority documents), these passage begins with "In another embodiment", and is not disclosed in combination with the instant size limitations or with the limitations of claims 19, 34, or 37. The specification contains a plethora of specific embodiments and does not appear to ever contemplate the specific genus as instantly claimed.

Therefore, the instant claims are accorded the priority date of 1/14/04, which is the filing date of the instant application, as further explained in the new matter rejection below.

Claim Rejections - 35 USC § 112

Claims 18-20 and 33-39 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention. This is a new matter rejection.

Claim 18 has been amended to require the combination of: each strand is 18-27 nucleotides in length, wherein 18-23 are complementary to each other and at least 18 nucleotides of the antisense strand are complementary to a target; in combination with

10 or more pyrimidine nucleotides of the sense and antisense strand being chemically modified with 2'-deoxy, 2'-O-methyl, or 2'-deoxy-2'-fluoro; and in combination with the elements of the dependent claims.

Upon a review of the instant specification, support is not evident for this particular combination of elements.

Although applicant points to support for the instant chemical modifications of claim 18 at page 30, lines 2-7 (as well as in the priority documents), these passage begins with "In another embodiment", and is not disclosed in combination with the instant size limitations or with the limitations of claims 19, 34, or 37.

The specification contains a plethora of specific embodiments and does not appear to ever contemplate the specific genus as instantly claimed.

MPEP §2163.06 notes:

> If new matter is added to the claims, the examiner should reject the claims under 35 U.S.C. 112, first paragraph - written description requirement. In re Rasmussen, 650 F.2d 1212, 211 USPQ 323 (CCPA 1981).

MPEP §2163.02 teaches that:

> Whenever the issue arises, the fundamental factual inquiry is whether a claim defines an invention that is clearly conveyed to those skilled in the art at the time the application was filed...If a claim is amended to include subject matter, limitations, or terminology not present in the application as filed, involving a departure from, addition to, or deletion from the disclosure of the application as filed, the examiner should conclude that the claimed subject matter is not described in that application.

A review of the specification does not reveal support for where the claim amendments are found. Should applicant disagree, applicants are encouraged to point

out with particularity by page and line number where such support might exist for the specific embodiment as instantly claimed.

There is no support for this claim limitation in the claimed priority documents. Therefore, the effective filing date of the instant claims is considered, for purposes of prior art, to be 1/14/04, which is the filing date of the instant application.

Claim Rejections - 35 USC § 103

Claims 18-20 and 33-39 are rejected under 35 U.S.C. 103(a) as being unpatentable over Elbashir et al. (The EMBO Journal, 2001, Vol. 20, No. 23, pages 6877-6888), in view of Matulic-Adamic et al. (US 5,998,203), Parrish et al. (Molecular Cell, Vol. 6, pages 1077-1087, 2000), and Crooke (US 5,898,031), for the reasons of record and as explained below.

It is noted that the references are of record and cited on the PTO-892 mailed on 12/21/06.

The invention of the above claims is drawn to a chemically modified double stranded nucleic acid comprising a sense strand and an antisense strand, wherein each strand is 18 to 27 nucleotides in length, 18 to 23 nucleotides of each strand are complementary to each other, and at least 18 nucleotides of the antisense strand are complementary to a target RNA sequence, and the sense strand comprises a terminal cap moiety at the 5' and 3' end. The invention is further drawn to specific terminal cap moieties, as well as modifications to the duplex and a composition comprising the double stranded nucleic acid and a pharmaceutically acceptable carrier or diluent.

Elbashir et al. (EMBO) teach siRNAs, wherein each strand is 21-23 nucleotides in length and wherein the sense strand is complementary to the antisense strand. Elbashir et al. teach chemical modification with 2'-deoxy or 2'-O-methyl modifications. Elbashir et al. teach modification of 19% of the nucleotides of a duplex 21 nucleotides in length with 2'-deoxy modifications.

Elbashir et al. teach duplexes with 2 nt 3' overhangs, as well as blunt ended duplexes wherein all 21 nucleotides are complementary between the sense and antisense strand. Elbashir et al. teach that duplexes 21 nucleotides in length with 2 nt 3' overhangs were the most efficient triggers of sequence-specific mRNA degradation. Elbashir et al. teach duplexes wherein the sense and antisense strands are complementary at 19 or 21 nucleotide positions (see for example, Figure 1D (1^{st} duplex) and Figure 1F (1^{st} duplex)). Elbashir et al. teach 2'-deoxythymidine in the 3' overhang (see page 6884). The 100% modified duplex taught by Elbashir et al. is considered to not comprise ribonucleotides.

Elbashir et al. do not teach double stranded nucleic acid molecules comprising the instantly recited terminal cap moieties and do not teach 2'-deoxy-2'-fluoro or phosphorothioate modifications. Elbashir et al. do not teach a composition comprising the double stranded nucleic acid molecule and a pharmaceutically acceptable carrier.

Matulic-Adamic et al. teach chemical modifications of double stranded nucleic acid structures. The enzymatic RNA molecules of Matulic-Adamic et al. are taught to be targeted to virtually any RNA transcript and achieve efficient cleavage (see column 1) and to be sufficiently complementary to a target sequence to allow cleavage. Matulic-

Adamic et al. teach the incorporation of chemical modifications at the 5' and/or 3' ends of the nucleic acids to protect the enzymatic nucleic acids from exonuclease degradation, which improves the overall effectiveness of the nucleic acid, as well as facilitates uptake of the nucleic acid molecules (see column 2). Matulic-Adamic et al. teach base, sugar and/or phosphate modification, as well as terminal cap moieties at the 5'-cap, 3'-cap, or both. Specifically, 3' phosphorothioates, inverted abasic moieties, and 2'-O-methyl modifications are utilized. Matulic-Adamic et al. teach 2'deoxy nucleotides and 2'-deoxy-2'-halogen nucleotides, wherein Br, CL and F are representative halogens (see column 3, for example). For example, figure 3 contains a ribozyme structure that encompasses modification of at least 20%, at least 30%, at least 40% or at least 50% of the nucleotide positions, as well as the modifications instantly claimed. The modifications can be in one or both of the strands and can be modifications of different types within the same structure.

Matulic-Adamic et al. teach that preferred caps include 4', 5'-methylene nucleotides, 1-(beta-D-erythrofuranosyl) nucleotides, 4'-thio nucleotides, 1,5-anhydrohexitol nucleotides, L-nucleotides, threo-pentofuranosyl nucleotides, acyclic 3', 4'-seco nucleotides, 3,4-dihydroxybutyl nucleotides, 3,5-dihydroxypentyl nucleotides, 3'-3'-inverted nucleotide moieties, 3'-3'-inverted abasic moieties, 3'-2'-inverted nucleotide moieties, 3'-2'-inverted abasic moieties, 5'-5'-inverted nucleotide moieties, and 5'-5'-inverted abasic moieties (see columns 3 and 4, for example). Matulic-Adamic et al. teach compositions comprising the nucleic acid and reaction buffer, which is a diluent.

Parrish et al. teach a chemically synthesized siRNA molecule, wherein each strand is 26 bp in length. Additionally, Parrish et al. teach a 742 nt long dsRNA with extensive modification with 2'-deoxy-2'-fluoro modifications, which resulted in successful RNA interference. Parrish teaches that the 2'-deoxy-2'-fluoro modifications incorporated into the long dsRNA produces unc-22 interference and furthermore described the interference as strong (+++, see figure 5).

Crooke teaches gapmer oligonucleotide chemistry and teaches that gapmer strategies increase oligonucleotide affinity to the target RNA (see column 9, for example). Crooke teaches chemical modifications that are incorporated to improve pharmacokinetic binding, absorption, distribution or clearance properties of the compound, affinity or specificity of the compound to target RNA, or modification of the charge of the compound (see column 7, for example).

Crooke teach that a particularly useful 2'-substituent group for increasing the binding affinity is the 2'-fluoro group (see column 12). Crooke also teaches 2'-O-methyl modifications.

It would have been obvious to synthesize a double stranded nucleic acid molecule with the structural characteristics taught by Elbashir et al., wherein the molecule is formulated in a composition with a diluent, as taught by Matulic-Adamic et al. It would have been obvious to incorporate the specific modifications taught by Parrish et al. and Matulic-Adamic et al.

One would have been motivated to synthesize a double stranded nucleic acid molecule, as taught by Elbashir et al. (EMBO), wherein the molecule is formulated in a

composition with a diluent, because Matulic-Adamic et al. teach successful inhibition of target gene expression with nucleic acid molecules formulated in a diluent. Furthermore, the reactions performed by Elbashir et al. require diluents such as buffers and water.

One would have been motivated to synthesize a double stranded nucleic acid molecule, as taught by Elbashir et al. (EMBO), with the modifications taught by Parrish et al. and Matulic-Adamic et al. because each of the modifications were known in the art to protect nucleic acids from exonuclease degradation, which improves the overall effectiveness of the nucleic acid, as well as facilitates uptake of the nucleic acid molecules, as taught by Matulic-Adamic et al. Additionally, Parrish et al. and Matulic-Adamic et al. teach extensive chemical modification of long dsRNA and ribozymes, respectively, with successful inhibition of target gene expression.

Since Elbashir et al. (EMBO), Matulic-Adamic et al., and Parrish et al. teach modified double stranded nucleic acid molecules that inhibit target gene expression, and Crooke teaches gapmer oligonucleotide chemistry to improve pharmacokinetic properties of the oligonucleotide, one would have been motivated to synthesize duplexes, as taught by Elbashir et al., with each of the instantly recited modifications, as taught by Elbashir et al., Matulic-Adamic et al., and Parrish et al. in order to optimize the activity of the molecule, as taught by Crooke.

Additionally, antisense oligonucleotides, ribozymes, and dsRNAs are each commonly used for sequence-specific mRNA knockdown and each of these encounters delivery problems for effective application. Therefore, one would have been motivated

to utilize the same modifications and techniques that have been utilized to overcome these problems with antisense oligonucleotides or ribozymes with siRNAs to add the same benefits to RNAi technology.

For example, Crooke teaches that gapmer oligonucleotide chemistry has provided antisense oligonucleotides with increased target affinity and pharmacokinetic properties. Crooke teaches that different modifications at different regions of the oligonucleotide have been tested in order to optimize oligonucleotide activity. Crooke teaches stepwise experimentation of modifications throughout oligonucleotides in order to find the optimal configuration. Crooke is relied upon as evidence that it is common to experiment with different known modifications at different locations to optimize oligonucleotide activity.

It would have been prima facie obvious to perform routine optimization to determine which of the known modifications or combinations of modifications are optimal. As noted in *In re Aller*, 105 USPQ 233 at 235,

> More particularly, where the general conditions of a claim are disclosed in the prior art, it is not inventive to discover the optimum or workable ranges by routine experimentation.

Routine optimization is not considered inventive and no evidence has been presented that the selection of the specific modifications used were other than routine, that the products resulting from the optimization have any unexpected properties, or that the results should be considered unexpected in any way as compared to the closest prior art.

Therefore, one would have been motivated to apply such a method to incorporate known modifications at various locations (i.e. regions/positions of duplex or pyrimidine v. purine) and amounts, as taught by Crooke, into the siRNA duplexes that were synthesized by Elbashir et al.

Finally, one would have a reasonable expectation of success given that each of the modifications were known in the art at the time the invention was made to add benefits to antisense oligonucleotides, ribozymes, dsRNAs or siRNA duplexes, as evidenced by Elbashir et al., Matulic-Adamic et al., Parrish et al. and Crooke, wherein each of the molecules face the same challenges, and each of which can be improved with modifications. Since Crooke teaches effectively walking modifications across antisense oligonucleotides to optimize the location of the modifications and activity of the oligonucleotide and Elbashir et al., Matulic-Adamic et al., and Parrish et al. teach successfully synthesizing modified double stranded nucleic acid molecules, one would reasonably expect for each of the modifications to benefit the double stranded nucleic acid molecules of Elbashir et al. as well. Furthermore, the long chemically modified dsRNA taught by Parrish et al. (that are necessarily cleaved by Dicer as they act via RNAi) further demonstrate that extensively modified dsRNA molecules result in RNA interference activity. Since Elbashir et al., Matulic-Adamic et al., and Parrish et al. teach modification of double stranded nucleic acid molecules and Crooke teaches experimentally determining optimal locations and levels of modification of antisense oligonucleotides, incorporating each of the modifications in the double stranded nucleic acid molecules of Elbashir et al. is considered within the realm of routine optimization.

It is noted that Elbashir et al. teach that 100% modification of one or both strands with 2'-deoxy or 2'-O-methyl modifications abolished activity. However, regardless of the results of these specific modifications at 100% of the positions of one or both strands, Elbashir et al. did modify duplexes and published data regarding successful inhibition with some duplexes and unsuccessful inhibition with others, supporting that testing of such known chemical modifications is routine in the art. The results of Elbashir et al. are considered to offer motivation to incorporate chemical modifications at various percentages to optimize the activity of the duplex because not all modifications result in activity at every percentage.

Thus in the absence of evidence to the contrary, the invention as a whole would have been prima facie obvious to one of ordinary skill in the art at the time the invention was made.

(10) Response to Argument

Claim Rejections - 35 USC § 112 (and Priority)

The specification clearly sets forth many different embodiments, none of which are equivalent or commensurate in scope with the instant claims. There is no cohesive link that would lead one to interpose the embodiments in the manner as claimed. While the specification discloses a multitude of specific embodiments, it does not describe how they would be related or combined to result in the instant genus. It does not appear that the specific claimed combination was contemplated.

Applicant points to the paragraph spanning pages 29 and 30 of the instant specification for support. However, the passage cited by applicant is supportive of part (d) only of claim 18. Applicant points to another embodiment on page 32, line 10, to support the length requirements although this passage clearly sets forth that such requirements are specific to chemical modification patterns of Formulae I-VII, none of which are identical to the instant genus. Applicant sets forth that Formulae I-VII collectively include each type of modification of the instant claims. However, each Formulae is a specific pattern of varying modifications, none of which are commensurate in scope with the instant claims. Applicant argues that the passage clearly refers to any siNA of the invention, however this is false, as the passage is closed to Formulae I-VII. Furthermore, it is noted that the claims are not directed to siNA molecules per se, but rather double stranded nucleic acid molecules.

Applicant points to Table IV, which sets forth modifications that are not commensurate in scope with the instant claim breadth, which requires 10 or more (total combined pyrimidine modifications between both strands) of specific types of modifications. The table is not representative of the instant claims because the instant claims do not specify what all pyrimidines or all purines are, as required by the table.

Response to Arguments-103

It is noted that the interpretation of the Elbashir et al. (TuschI) reference is argued in detail by applicant. However, the interpretation of the article has already been decided by the Board in the related appeal (Reexamination control 90/008,177, Patent 7,022,858), and the interpretation is consistent with that of the examiner in the instant rejection.

On page 27 of the decision, the board sets forth that appellant's argument that TuschI teaches avoiding any 2'-O-methyl modifications is unpersuasive and misstates the teachings of TuschI. A fair reading is that more extensive 2'-deoxy or 2'-O-methyl modification beyond the two nucleotide 3'-overhang reduces the ability of siRNAs to mediate RNAi. Stating that complete substitution abolished RNAi is not the same of stating that any 2'-O-methyl modification should be avoided. It is noted that when incorporating chemical modifications into nucleic acid inhibitory molecules, it is routine to balance stability and activity. Therefore, it is a matter of routine optimization to

determine an acceptable balance between a reduction in activity and an increase in stability, as long as the molecule is still in fact active.

The decision also sets forth that nucleic acid molecules are known to be degraded or hydrolyzed by nucleases *in vivo* and in culture systems and thus it is routine in the art to modify nucleic acids to resist nuclease hydrolysis, and particularly to modify with modifications that were known to enhance stability. Similarly, capping as disclosed by Matulic-Adamic et al. would be reasonably expected to sterically interfere with the active site of a nuclease (see page 25 of decision, for example).

Applicant argues that the state of the art at the time of the invention only provided double stranded molecules that were useful as research tools *in vitro* due to lack of serum stability. The basis of applicant's argument is unclear given that applicant was certainly not the first to provide double stranded molecules for use *in vivo*. Furthermore, it was known that chemical modifications aid in the stability of double stranded molecules for *in vivo* use (see for example McCaffrey et al., Nature, Vol. 418, July 4, 2002, pages 38 and 39).

Applicant sets forth that this significant advancement over the prior art has been diminished by the examiner via referring to it as a matter of routine optimization. Again, the basis of applicant's argument is unclear given that the claims do not require any specific function and that applicant was not the first to utilize double-stranded molecules for in vivo use. This argument is completely askew for the rejection of record, which does not address such because these are not elements of the claims. The matter of routine optimization is combining specific chemical modifications that are routinely used

to enhance the activity of nucleic acid inhibitory molecules in a manner that renders the instant genus obvious, given that applicant has shown no unexpected property for such a genus.

Applicant argues that there would not have been a reasonable expectation of success. Contrary to applicant's argument, this is not true given the instantly claimed genus. It was well within the technical grasp of the skilled artisan to combine chemical modifications that were known and routinely used to enhance stability of nucleic acid therapeutic molecules to arrive at molecules within he instantly claimed genus that would likely have activity, as it was known in the art to balance stability and activity via routinely testing different combinations/quantities of such modifications.

Applicant argues that teachings of the Elbashir et al. reference, which as set forth above, has already been interpreted by the board in the same exact way as interpreted by the examiner.

It is noted that the only modification schematic that is taught away by Elbashir et al. is 100% modification of one or both strands with one type of modification, either 2'-deoxy or 2'-O-methyl. This does not teach away from incorporation of any other type or combination of modifications and does not teach away from 2'-O-methyl or 2'-deoxy modifications at any other percentages. It is believed that applicant's arguments directed to Elbashir et al. have been addressed in detail. Given that Elbashir et al. is evidence that there is a need to balance stability and activity via incorporating different levels of modification, one would have been motivated to combine the modifications at varying positions, which was not done by Elbashir et al.

Applicant continues to argue the teachings of this reference via drawing their own conclusions as to results between the 19% successful modification and 100% unsuccessful modification of Elbashir et al., experiments that simply are not addressed via Elbashir. Applicant points to page 6885 of Elbashir et al. and interprets the passage as teaching away from producing extensively modified duplexes. This passage is interpreted by both the examiner and the board as referring to the only extensive modification that is taught by Elbashir et al., which is 100% modification. Elbashir et al. is completely silent as to modification between 8/42 positions that was successful and 100% modification with a single type of modification that was unsuccessful.

Importantly, the instant claims are not directed to any specific target sequence and only require 10 pyrimidine modifications collectively between both strands. Therefore, depending on the target sequence, the diminimus of the instant claim breadth is only a difference between one modification on each strand because Elbashir et al. teaches the incorporation of 8 modified positions. Therefore, although applicant continues to argue that Elbashir et al. teaches away, this simply is not the case.

The only modified duplexes that exhibit abolished activity in the Elbashir et al. reference are 100% modified. Elbashir et al. is evidence that incorporation of such chemical modifications into siRNA molecules results in active molecules in some configurations and inactive molecules in others, supporting that routine optimization is needed. Furthermore, Elbashir et al. is evidence that modification is well tolerated in the terminal portions of the duplex, offering further motivation to modify the terminal regions. Elbashir et al. teaches that some modification does not affect RNAi, but helps

to reduce the cost of RNA synthesis and may enhance RNase resistance of siRNA duplexes (see page 6885, column 1). Applicant argues that Elbashir only succeeded at modifying a single terminal region on each strand. Importantly, this is all that Elbashir et al. tested and therefore does not teach away from incorporating terminal modifications at the other end. Since the modifications were tolerated on the one end, one would have been motivated to incorporate them on the other end. Again, applicant is not claiming any specific configuration of modifications, but is rather claiming a genus of modification types or combinations thereof at various positions depending on the target sequence.

Applicant also argues that Parrish et al. teaches away. It is noted that applicant argues that the references teach away but do not set forth how they in fact teach away from the instant claim breadth, which is not closed to any specific pattern. As evidenced by Matulic-Adamic et al. and Parrish et al., it was known to incorporate extensive modification into nucleic acid inhibitory molecules, wherein the molecules of Parrish et al. act via RNAi.

Applicant argues that Parrish et al. teaches that some modifications resulted in instability whereas others were compatible, depending on the location and extent to which the modification was applied, which is again supportive of the instant position that routine optimization is needed to determine the optimal configuration for the instant modifications. Parrish et al. teaches extensive modification of a long dsRNA with 2'-deoxy pyrimidine modifications with resultant interference activity. Although applicant argues that this is a misstatement of the teachings of Parrish, this is explicitly taught by

Parrish. It is noted that the dsRNA molecules of Parrish et al. were extensively modified and resulted in strong RNAi activity. Applicant argues that Parrish et al. teaches away from incorporating 2'-deoxy modifications and that this point is ignored by the office. The basis of this argument is unclear given that the examiner has pointed specifically to data of Parrish et al. wherein a long dsRNA with 2'-deoxy pyrimidine modifications with resultant interference activity.

Applicant argues that Parrish et al. teaches that modification of cytidine to deoxycytidine on either strand produced a substantial decrease in activity. Applicant is arguing elements that are not claimed. Furthermore, the molecule referred to by applicant resulted in a decrease in activity but was in fact still active. As set forth above, it is routine in the art to balance stability and activity, often accepting a level of loss of activity for the benefit of enhanced stability. The balance of these two properties is the element that is routine optimization. Furthermore, the instant claims are compound claims that do not require any specific activity.

Applicant argues that Parrish teaches away from applying more than one phosphorothioate modification. However, claim 18 does not require and phosphorothioate modifications and claim 39 only requires one phosphorothioate modification. Therefore, applicant's assertion that Parrish teaches away is unfounded.

Applicant sets forth a citation from the Parrish et al. reference and points to page 1084. Upon a review of the document, it appears that applicant is referring to a statement on page 1081 of Parrish. The passage teaches that Zamore et al. have noted a preference for U residues in RNA-associated cleavage in vitro and RNAs with

two modified bases also had substantial decreases in effectiveness as RNAi triggers. This teaching in no way is commensurate in scope with the instant claims or relevant to applicant's argument regarding teaching away from the instant claim breadth.

Although applicant argues limitations that are not required by the instant claims, Parrish et al. does teach extensive pyrimidine modification with strong RNAi activity (see Figure 5 on page 1081), thus offering motivation to extensively modify at various positions. Applicant has not set forth arguments against the teaching of Parrish et al. regarding extensive pyrimidine modification of a dsRNA molecule with strong RNAi activity.

Applicant argues that the examiner uses impermissible hindsight to support the assertion that one of skill would have had a reasonable expectation of success in generating highly modified duplexes that retain RNAi activity. Although applicant continues to argue motivation to extensively modify, the instant claims require a total of 10 pyrimidine modifications out of a total of 27 nucleotides. Applicant argues elements that are not claimed. Furthermore, the claims are directed to incorporation of modifications that are each known in the art to enhance stability of nucleic acid inhibitory molecules at a large genus of possible combinations/positions (based upon target sequence) with no required activity. With regards to pyrimidine modifications, Parrish et al. teaches extensive pyrimidine modification with strong interference activity and there are only two choices of places to modify, purine or pyrimidine.

Applicant argues that after walking modifications, as described by Crooke, across a dsRNA molecule, Elbashir concluded that more extensive modification was not

favored. Contrary to applicant's argument, Elbashir does not teach walking modifications, but rather teaches a specific experiment with incorporation at 8/42 positions with a single type of modification or 100% modification with one type of modification. Also, Elbashir does not teach to avoid extensive modification commensurate with applicant's sweeping statement, but rather teaches to avoid 100% modification with 2'-deoxy or 2'-O-methyl modifications and supports this specific example with data.

Applicant sets forth a hypothetical walking experiment, which is applicant's own interpretation of what one would do based upon the teachings of the prior art but does not in any way negate the motivation in the art to incorporate the instant modifications to enhance stability of siRNA molecules. Regarding cap modifications, caps were routine in the art, as evidenced by Matulic-Adamic et al. Applicant is combining elements of the prior art that were each known to enhance stability of nucleic acid molecules.

The instant specification discloses a multitude of oligonucleotide and ribozyme art regarding chemical modifications and teaches that "Such publications describe general methods and strategies to determine the location of incorporation of sugar, base and/or phosphate modifications and the like into nucleic acid molecules without modulating catalysis, and are incorporated by reference herein. In view of these teachings, similar modifications can be used as described herein to modify the siNA nucleic acid molecules of the instant invention so long as the ability of siNA to promote RNAi in cells is not significantly inhibited." (see page 112).

It is acknowledged that the specification is not to be relied upon for a source of motivation and that is not considered to be the instant case. The specification is merely being relied upon to distinguish that applicant recognized that double stranded nucleic acid modification is dependent upon the state of the art of oligonucleotides and ribozymes and that previously beneficial chemical modifications would be used with double stranded nucleic acid molecules as well.

Applicant argues that the instant claims are directed to nucleic acid molecules with extensive modifications at specific positions and specific types of nucleotides. It is noted that the only position specific modification that is instantly claimed are terminal caps, which by nature are located in terminal positions. It was known and routine in the art to incorporate terminal cap moieties into nucleic acid inhibitory molecules, as set forth in the instant rejection. Regarding types of nucleotides, there is a finite number of choices for the modifications of the prior art to be incorporated at, purines or pyrimidines. It is certainly within the realm of routine optimization/design choice to incorporate the modifications at a purine or a pyrimidine, given that there are only two choices. Furthermore, the claims are not directed to any specific pattern of modification that has demonstrated any unexpected property, given that the claims embrace combinations of modifications at different positions depending on the target sequence. The quantity of purines or pyrimidines is entirely target sequence specific, although the instant claims are not closed to any specific target.

Applicant argues that the instant invention consists of novel and non-obvious combinations of features giving rise to surprising and unexpected results. Contrary to

applicant's argument, applicant has not demonstrated any unexpected result of the instantly claimed genus. One would expect incorporation of 10 pyrimidine modifications, wherein the position is dependent on the target sequence, within a dsRNA molecule of the instant size range to yield some level of activity, given that this is only 2 more modifications then demonstrated by Elbashir et al. The instant modifications can be selected from 2'-deoxy, 2'-O-methyl, or 2'-deoxy-2'-flouro (or any combination thereof), which are each very common modifications in the nucleic acid inhibitor art, more specifically in the dsRNA art, as evidenced by Elbashir et al. and Parrish et al.

Each of the chemical modifications were known in the nucleic acid inhibitor art to impart beneficial stability properties to such nucleic acid inhibitors. Furthermore, it was known in the art that testing/optimization is needed to determine optimal configurations of the modifications within the inhibitory molecules, as evidenced by Elbashir et al. and Crooke. Although applicant asserts that the examiner has cherry picked the modifications from the art, each of the modifications are equally obvious in view of the teachings of the prior art and these three are quite routine in the art, as evidenced by Elbashir et al. and Parrish et al. Furthermore, applicant is not claiming any specific configuration of any specific modifications, but is rather claiming a huge genus of combinations of possible chemical modifications and schematics thereof that are target sequence specific for the positions.

It is noted again that there are only two options to incorporate the instant modifications, purine or pyrimidine; and the instant claims require a total of 10

modifications out of a possible 27 positions. Applicant continues to broadly argue "extensive" modification, rather than directing the arguments to the instant claim scope.

Applicant points to *KSR International Co. v. Teleflex Inc.* (127 S. Ct. 1727 (2007)) to argue that the instant claims are directed to a new combination wherein the result cannot be predicted. As explained above, the instant claims are directed to a huge genus of modifications and combinations thereof, wherein the schematic is entirely target sequence specific. One would have been motivated to combine the prior-art elements and expect active molecules within the instant claim breadth. It is well within the grasp of the skilled artisan to select and combine known elements within the instant huge genus and to expect active molecules upon routine optimization of the placement of such modifications given the teachings in the nucleic acid inhibitor art. It is the routine optimization of the placement of the modifications that is relied upon for determining activity of such molecules, as it was known to perform such routine testing, as evidenced by Elbashir et al. and Crooke.

In view of *KSR International Co. v. Teleflex Inc.*, when a combination of admittedly old elements produces a new and beneficial result never attained before, it is evidence of invention. However, in the instant case applicant is not claiming any specific combination or modification schematic that produces an unexpected result, but is rather claiming a huge genus of possible molecules wherein molecules within the genus are certainly considered obvious in view of the teachings of the prior art.

The mere selection of elements from various prior art references and combining them together with no new function is an obvious use of common sense by one skilled in the art and therefore not patentable.

One of skill in the art would reasonably expect for the modifications of Matulic-Adamic et al. to likely benefit the molecules of Elbashir et al. as well. As explained above, the motivation need not be the same motivation set forth by applicant, but rather the motivation to enhance the stability of the molecules as set forth by Matulic-Adamic et al. Elbashir et al. teaches that preferred molecules are modified in the 3' terminal regions. Therefore, one would reasonably expect for the terminal cap moieties of Matulic-Adamic et al. to enhance the stability of the molecules of Elbashir et al. as well.

Applicant points to specific species within the instant genus in the instant specification and compares the molecules to those of Elbashir et al. Again, the instant genus is huge depending on the target sequence and combination/quantity of each type of the instants modifications. Armed with not only the teachings of Elbashir et al., but the combined teachings of each of the instantly cited references, the skilled artisan would have been motivated to incorporate the modification in different combinations and locations within the duplex within the instant genus and would expect to result in active molecules. The unmet need, as required by KSR, is that of balancing stability and activity with known chemical modifications.

Regarding Giese (US 2004/0180351), the instant claims are accorded an effective filing date of 1/14/04, whereas Giese was filed on 8/5/03. Applicant argues that the examiner's assertion that Giese provides evidence of routine optimization flies

in the face of the office's own determination of patentability. Applicant's argument is in error because Giese et al. claimed a specific static pattern of a specific modification that demonstrated preferred properties, whereas the instant claims are directed to a large genus of possible patterns depending on the target sequence and the 10 positions that are selected to modify, wherein applicant has not demonstrated any unexpected property or activity of such a broad genus. The testing that Giese set forth to arrive at an actual preferred pattern demonstrates that routine optimization is needed in the testing process. Therefore, applicant is claiming a broad genus, whereas Giese claimed a species.

Giese et al. teach that in addition to the various modifications or designs of the inventive RNAi molecules, further or additional modification of the nucleotides may include the use of a phosphorothioate backbone of the RNAi molecules which may be either complete or partial in order to inhibit endonuclease function (see paragraph [0170]).

Giese et al. teach that 2'-O-alkyl modifications stabilize RNAi molecules against degradation, but to a certain degree this is counterbalanced by the effect that 2'-alkyl modifications generally result in a reduced knockdown activity. Therefore, Giese et al. offers motivation to incorporate 2'-O-alkyl modifications in specific locations, rather than to blanket the siRNA with such modifications, consistent with the teachings of Elbashir et al. Giese et al. offers motivation to incorporate such modifications in a manner that is minimal enough to not reduce knockdown activity. Giese et al. teach that accordingly, the design of RNAi molecules has to balance stability against activity (see paragraph

[0176]). Giese et al. teach that the most efficient molecules were modified at alternating positions of both strands.

Giese teaches incorporation of various 2'-position modifications including amino, fluoro, methoxy, alkoxy, and alkyl (see paragraph [0024]). Giese teaches siRNA molecules wherein each strand comprises a plurality of groups of modified nucleotides having a modification at the 2'-position whereby each group of modified nucleotides is flanked on one or both sides by a flanking group of nucleotides, wherein the flanking group is either unmodified or is modified with a different modification than the modified groups (see paragraph [0025]).

Giese et al. teach siRNAs with various end modifications on the sense and antisense strand and particularly teach the sense strand should be modified at the 5' end to reduce off-target effects mediated by an otherwise functional sense strand which results in increased specificity of the siRNA which is advantageous for any medical use of the RNAi molecules or any target validation using the siRNA (see paragraphs 0103 and 0173).

Therefore, Giese et al. is further evidence that combining modifications in regions, including the instant types of chemical modifications is a matter of routine optimization of the balance of stability/activity, and that this is a better approach than blanketing the molecule with one type of modification.

Applicant argues the Elbashir et al. reference again and sets forth that Elbashir attempted to stabilize molecules but failed in providing molecules that are stable and active. The basis of this argument is unfounded given that Elbashir et al. does teach

active molecules that are modified. It is believed that the examiner has explained exhaustively that Elbashir et al. does not teach away from the instant claim scope in any manner, which is supported by the interpretation by the board.

Applicant in turn argues that the minimal requirements of claim 18 differ substantially from Elbashir. It is noted that Elbashir did not attempt the instant requirements, hence the instant rejection under 35 USC 103(a) rather than 35 USC 102 and supportive of Elbashir et al. not teaching away. Applicant sets forth one specific species within the instant genus as an example (see page 27 of the appeal brief) and argues that based upon that example, the instant claims are directed to a specific pattern with an unexpected result. The example set forth is based upon one specific location of one specific target, whereas the pyrimidine quantity and location of each strand is based upon target sequence and activity/stability of any given molecule will vary depending on the location and quantity of the modifications. This showing is simply not commensurate in scope with the instant claim breadth. This example does not even demonstrate all possible schematics within the instantly claimed genus with regards to this one duplex. The examiner has not asserted that such modifications should be freely and without limitation incorporated, but rather that it would have been obvious to incorporate the modifications with the motivation of enhancing stability, although it is recognized that optimization is needed to result in active molecules. Furthermore, the instant claims are compound claims with no specific function required.

(11) Related Proceeding(s) Appendix

Copies of the court or Board decision(s) identified in the Related Appeals and Interferences section of this examiner's answer are provided herein.

For the above reasons, it is believed that the rejections should be sustained.

Respectfully submitted,

/AMY BOWMAN/

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